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A review of the Marx protocols: prevention and management of osteoradionecrosis by combining surgery and hyperbaric oxygen therapy

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INTRODUCTION

Advances in surgery and radiotherapy in head and neck malignancies have resulted in a significant improvement in the rate of survival. Unfortunately this often leaves an aftermath of severe facial disfigurement and oral incontinence. Reconstructive efforts in an irradiated field are frequently complicated by wound dehiscence and infection so that ultimately, many patients become social outcasts. In addition 5 to 10 per cent of patients that have received high doses of therapeutic radiation develop osteoradionecrosis (ORN) over the ensuing years – either spontaneously or as a result of a simple tooth extraction in the irradiated jaw. The cost of managing osteoradionecrosis is staggering in addition to often being unsuccessful. Many patients with ORN, due to ongoing suffering from intractable, inoperable pain and malnutrition, eventually also succumb to substance abuse and drug dependance.

Various protocols have been suggested for the management of this notorious disorder and have met with variable and often inconsistent outcomes (Marx, 1983a). Dr Robert Marx, a maxillofacial surgeon of Miami University has researched the field of radiation tissue damage and osteoradionecrosis extensively, and has treated in excess of 400 patients with this disorder over the past 20 years. His protocols for combining hyperbaric oxygen therapy (HBO) and surgery in the prevention and management of osteoradionecrosis have become the standard of care (Marx, Johnson and Kline, 1985).

IRRADIATION TISSUE DAMAGE

Since 1983 the pathophysiology of the irradiated wound has been better defined (Marx, 1983a). It is now understood to be a sequence of events following radiation: a gradual and progressive obliterative endarteritis and cellular dysfunction leads to a hypoxic, hypovascular and hypocellular (3-H) tissue (Marx, 1983a, 1983b, 1988, 1994). This tissue is vulnerable and may eventually undergo spontaneous breakdown due to an imbalance between cell death and collagen lysis versus cell replacement and collagen formation. The end result is a non-healing wound of which the metabolic demands for healing and homeostasis exceed the oxygen and vascular supply (Marx, 1983a; Johnson, Marx and Buckley, 1992). Hyperbaric oxygen therapy (HBO) has demonstrated a unique ability to reverse some of the cellular changes and restore micro-vascular density to within 75-85 per cent of normal (Marx, 1990). This restores the tissue's ability to heal and affords the clinician with surgical, dental and reconstructive options that would otherwise be impossible or unpredictable (Johnson, Marx and Buckley, 1992). Although the overall incidence of ORN is low, the risk multiplies whenever surgical wounding occurs within 21 days of commencing radiotherapy or after 4 months following radiotherapy. The threshold radiation dose above which the risk for ORN increases dramatically is 60 gray (Johnson, Marx and Buckley, 1992). The gray (Gy) is the amount of absorbed radiation in any tissue and applies to all types of radiation. For practical purposes 1000 rads (R) is equal to 10 gray.

PREVENTION OF OSTEORADIONECROSIS (20/10 PROTOCOL)

All patients that have received > 60 Gy to the jaw are at a risk of eventually developing ORN (Marx, 1983a, 1983b, 1988, 1990, 1994; Johnson *et al*, 1992). Due to the unique nature of the radiated wound, it never heals or revascularises normally and is at risk for spontaneous or trauma-induced breakdown (Marx, 1983b). Three types of osteoradionecrosis have been identified (Marx, 1983b, 1988; Marx *et al*, 1995):

a. **Type 1 ORN** occurs when the time between a dental or an extirpative surgical procedure and radiotherapy is too short. Typically this involves radiotherapy within 21 days of tooth extraction or mandibulotomy. The risk for developing ORN is very high if radiotherapy is commenced within 14 days of surgery. If at all possible, mandibulotomies should also be planned outside the irradiated field. Tooth extraction during radiotherapy must be avoided at all costs. Within the first 4 months following radiotherapy – the so-called golden period, healing usually occurs normally. Dentectomies and other surgical procedures can usually be performed without complications and HBO is not required in the prevention of ORN within this period. HBO is not routinely indicated in the management of acute radionecrosis or radiation burns.

b. **Type 2 ORN** is trauma induced. It mainly occurs three to six years after radiotherapy, typically following the extraction of a tooth.

c. **Type 3 ORN** occurs spontaneously following radiotherapy. It is associated with higher radiotherapy doses, neutron beam therapy or brachytherapy and occurs six months to two years after radiotherapy.

The overall incidence of ORN in irradiated patients is low (5–10 per cent). However, in patients who have received > 60 Gy and require surgery or tooth extractions, it is high; 89 per cent of all trauma induced ORN occurs secondary to tooth removal in the period 6 months to 3 years following radiotherapy.

In a study by Marx *et al* (1990), 74 patients requiring dentectomies with an average dose of 72 Gy were randomised in two groups: The first group received 20 HBO treatments before extraction and 10 HBO treatments thereafter. In this group the incidence of ORN after six months was 5,4 per cent (n=2). In the non-HBO (penicillin) group the incidence was 29,9 per cent (p=0,005). However, 8 of the 11 patients in the non-HBO group that developed ORN required jaw resections. Neither of the two HBO patients required resections, indicating that even where ORN did occur after HBO, it was less severe and could be treated by simpler and less expensive means than where HBO was not given.

If more than 4 months has elapsed since the last course of radiotherapy, 20 daily HBO treatments should be given before performing any surgery in an irradiated field, including dentectomies (Marx, 1983a, 1994; Johnson *et al*, 1992). Pre-surgical HBO treatment reverses the vascular changes of radiotherapy and restores vascular density to between 75-85 per cent of normal after 18 to 23 treatments. After surgical wounding, an additional 10 treatments of HBO are recommended to ensure uncomplicated healing. This protocol has become the standard of care since 1985 in the US. Although this approach may seem expensive, the cost of managing ORN (once established) is infinitely greater and frequently unsuccessful.

The prognosis of mandibular reconstruction in an irradiated field has improved from a 40-50 per cent chance of success without HBO to a 90–93 per cent chance with the 20/10 protocol (Marx, 1994).

Free micro vascular flaps that are brought into an irradiated field, although independent in their own blood supply, must still heal into the irradiated tissue. Eventually many flaps are lost when this does not occur. In a detailed randomised, prospective study by Marx – looking at wound dehiscence, infection and delayed healing in 160 patients with soft tissue reconstruction using vascularised flaps in an irradiated field (>64 Gy), the following results were obtained (Marx, 1994): incidence of dehiscence 11 per cent (HBO) versus 48 per cent (Non-HBO) p= 0,001; infections: 6 per cent versus 24 per cent; delayed healing: 11 per cent versus 55 per cent . Delay in healing was measured as extended hospitalisation required specifically by the non-healing irradiated wound.

Osseointegrated implants present two problems when inserted in irradiated bone: failure to integrate and precipitation of ORN. By using the 20/10 protocol in conjunction with implant insertion, the success rate of integration has been 83-86 per cent (compared to 94 per cent in normal bone) with no precipitation of ORN (Marx, 1994).

Summary
The 20/10 protocol is of great benefit in the prevention of ORN or soft tissue necrosis to all patients undergoing surgical procedures in a > 60 Gy irradiated field after 4 to 6 months of completing the radiotherapy. If possible, surgical procedures to the mandible should also be avoided within 21 days of commencing radiotherapy.

MANAGEMENT OF OSTEORADIONECROSIS (30/10 PROTOCOL)

Once radiological osteolytic changes are visible or alveolar bone has remained exposed for more than 6 months in an irradiated field, the clinical diagnosis of osteoradionecrosis can be made (Marx, 1983a, 1994). ORN, is not an osteomyelitis. In a study by Marx in 1983, comparing cultures from mandibular ORN and osteomyelitis patients, he clearly demonstrated that ORN was a radiation osteomyelitis as previously conceived (Marx, 1983b).

The only cost effective way to manage ORN is to eradicate the disease. This means that all necrotic bone has to be removed. As the trauma of debridement and sequestrectomy may lead to further propagation of the necrosis, pre-HBO surgery in an irradiated mandible is contra-indicated. All patients should receive 30 daily sessions of hyperbaric oxygen therapy (5 days a week) before any surgery is performed. This preserves and improves the vascularity of any viable bone adjacent to the ORN before debridement or resection. Early surgery before HBO reduces the chances of resolving the disease in a milder form (earlier stage). Pre-operative HBO will also better define the margin between necrotic and healthy bleeding (viable) bone intra-operatively (Marx, 1994; Johnson *et al*, 1992). The final 10 HBO treatments ensure that the viable bone remains viable post-operatively and also supports the primary closure of the gingiva after debridement or resection, thereby preventing the complications of infection or dehiscence.

As the clinical presentation of ORN may range from slight radiological osteolytic changes to a pathological fracture or orocutaneous fistula, it is important to carefully plan the type of surgery that will be required in combination with HBO to provide the best, most cost effective and predictable results. To achieve this goal, Marx has proposed a system of staging the disease to better define surgical management of ORN.

Staging

Staging is done to optimise the type of surgical intervention required, depending on the severity of the disease. Staging is dynamic (i.e. patients not responding to Stage 1 are advanced/reclassified to Stage 2 or Stage 3) and is based on the following selection criteria (Marx, 1988, 1994; Johnson *et al*, 1992): All patients are initially entered as Stage 1. Exceptions to this are patients with orocutaneous fistulae, pathological fractures through the mandible or those with resorption/osteolysis of the inferior border of mandible who are managed as Stage 3, i.e. discontinuity resection of the mandible (see below).

Stage 1

Stage 1 ORN usually presents with mild or no osteolytic changes and exposed alveolar bone. Antibiotics are not usually required but may be administered when there is evidence of soft tissue infection. No surgery is performed other than irrigation and removal of bone fragments. After 30 treatments the tissue is reassessed. If the bone has softened and there are good signs of granulation tissue, the patient is classified as a Stage 1 responder. These patients require no or only minimal surgery after which they receive the final 10 HBO treatments. If the exposed bone does not respond, the patient is classified as a Stage 1 non-responder and advanced to Stage 2. Fifteen per cent of patients with ORN resolve as Stage 1.

Stage 2

Stage 2 ORN patients (or Stage 1 non-responders) will already have received the initial 30 HBO treatments. They differ from Stage 1 ORN in that the extent of the disease is greater and requires more aggressive transoral surgery, sequestrectomy or partial resection of the mandible. Stage 2 treatment still maintains the continuity of the mandible. Fifteen per cent of patients with ORN resolve as Stage 2 (Marx, 1994; Johnson *et al*, 1992).

Stage 3

Stage 3 ORN patients are those failing Stage 2 management, or those admitted with orocutaneous fistulae, pathological fractures or evidence of resorption or osteolysis of inferior border of mandible. These patients require a discontinuity resection of the mandible back to bleeding bone and bleeding soft tissue (Johnson *et al*, 1992). After the resection, maxillo-mandibular relationships need to be maintained by one of two methods. Ideally the Joe-Hall-Morris pin fixation should be used as suggested by Marx (1994) or maxillo-mandibular wiring may be used. Rigid internal fixation plates must not be used or be used very cautiously as exposure of the plates frequently occurs. Intra-operatively the soft tissue may be reconstructed (if resection has created a defect) by way of a free vascular transfer or myocutaneous flap, if there is no overt infection (Marx, 1994). The pectoralis major myocutaneous flap is the one that has provided consistently the best results in Marx' experience (Marx, 1988, 1994; Johnson *et al*, 1992). Following resection and/or soft tissue reconstruction, the last 10 HBO treatments are given to complete the 30/10 protocol. Patients requiring bony reconstruction are usually grafted at three months post-resection (Marx, 1994; Johnson *et al*, 1992). Allogenous split rib or hollowed out mandible, packed with densely packed autologous cancellous bone, has proven to be the most effective in Marx' experience (Marx, 1983a; Marx and Kline, 1983; Johnson *et al*, 1992). Such graft procedures may be provided without further HBO as the angiogenesis and fibroplasia are long lasting and need not be reinforced (Marx, 1990). If there are intra-operative complications or the quality of the recipient bed seems inadequate, a further 10 hyperbaric treatments may be given. Sixty-four per cent of patients resolve as Stage 3.

Summary

The 30/10 protocol is employed in the treatment of established osteoradionecrosis. No surgery should be attempted before the first 30 HBO treatments have provided sufficient angiogenesis to support surgical wounding. After 30 treatments surgical management can be staged according to the extent of improvement achieved after HBO and the size of sequestrum or area of osteolysis. If the ORN extends to the inferior border of the mandible or if it manifests as an orocutaneous fistula or pathological fracture, discontinuity resection of the necrotic bone and soft tissue will be required to resolve the disease. Unless HBO and surgery are combined in the management of ORN, the results are not long lasting or satisfactory. Even though resection of stage three ORN seems unduly aggressive, it has stood the test of time. By using the Marx protocols in the treatment of ORN, more than 95 per cent of patients can be successfully cured of their disease with predictable, functional and aesthetically acceptable outcomes.

REFERENCES

Johnson, RP, Marx, RE & Buckley SB (1992) Hyperbaric Oxygen in oral and Maxillofacial Surgery In: Controversies in Oral and Maxillofacial Surgery. Worthington P & Evans JR (Eds). London: WB Saunders Co. pp. 107-126

Marx, RE, (1983a) A new concept in the treatment of osteoradionecrosis. *Journal of Oral Maxillofacial Surgery*, **41**, 351-357

Marx, RE, (1983b) Osteoradionecrosis: A new concept in its pathophysiology, *Journal of Oral Maxillofacial Surgery*, **41**, 283-288

Marx, RE & Kline SN (1983) Principles and methods of osseous reconstruction. In: *International Advances in Surgical Oncology*. AP Murphy (Ed). 167-228. New York: Alan R Liss Inc.

Marx, RE. (1988) Problem wounds in oral and maxillofacial surgery. In: *Problems Wounds The Role Of Oxygen*. JC Davis & TK Hunt (Eds) The role of hyperbaric oxygen. New York: Elsevier Science Publication Co. 4, 65-123

Marx, RE, Ehler, WJ, Tayapongsak, PT, & Pierce, LW, (1990) Relationship of oxygen dose to angiogenesis induction in the irradiated and tissue deficient patient. *American Journal of Surgery*, **160**, 519-524

Marx, RE, Johnson, RP, & Kline, SN. (1985). Prevention of osteoradionecrosis: A randomised prospective clinical trial of hyperbaric oxygen versus penicillin. *Journal of the American Dental Association*, **111**, 49-54

Marx, RE. (1994) Radiation Injury to tissue. In: *Hyperbaric Medicine Practice*. EP Kindwall (Ed.) Flagstaff: Best Publishing Co. pp.448-503.

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